

Intake of Flavonoids, Carotenoids, Vitamins C and E, and Risk of Stroke in Male Smokers

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Background and Purpose—Antioxidants may protect against atherosclerosis and thus prevent cerebrovascular disease. We studied the association between dietary antioxidants and subtypes of stroke.

Methods—The study cohort consisted of 26 593 male smokers, aged 50 to 69 years, without a history of stroke. They were participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland. The men completed a validated dietary questionnaire at baseline. Incident cases were identified through national registers.

Results—During a 6.1-year follow-up, 736 cerebral infarctions, 83 subarachnoid hemorrhages, and 95 intracerebral hemorrhages occurred. Neither dietary flavonols and flavones nor vitamin E were associated with risk for stroke. The dietary intake of β -carotene was inversely associated with the risk for cerebral infarction (relative risk [RR] of highest versus lowest quartile 0.74, 95% CI 0.60 to 0.91), lutein plus zeaxanthin with risk for subarachnoid hemorrhage (RR 0.47, 95% CI 0.24 to 0.93), and lycopene with risks of cerebral infarction (RR 0.74, 95% CI 0.59 to 0.92) and intracerebral hemorrhage (RR 0.45, 95% CI 0.24 to 0.86). Vitamin C intake was inversely associated with the risk for intracerebral hemorrhage (RR 0.39, 95% CI 0.21 to 0.74). After simultaneous modeling of the antioxidants, a significant association remained only between β -carotene intake and risk for cerebral infarction (RR 0.77, 95% CI 0.61 to 0.99).

Conclusions—Dietary intake of β -carotene was inversely associated with the risk for cerebral infarction. No association was detected between other dietary antioxidants and risk for stroke. (*Stroke*. 2000;31:2301-2306.)

Key Words: antioxidants ■ diet ■ epidemiology ■ stroke

Consumption of fruits and vegetables has been shown to be associated with a lowered risk for stroke.^{1,2} This may result from fruits and vegetables being rich in several antioxidants, which are known to be effective scavengers of free radicals.³ Antioxidants could, therefore, protect low-density lipoproteins from oxidation and slow the formation of atherosclerotic plaques.⁴ Other mechanisms by which antioxidants could protect from stroke are reduction of platelet aggregation (especially flavonoids⁵ and vitamin E)⁶ and lowering of blood pressure (especially vitamin C).⁷ However, results on specific antioxidants in fruits and vegetables have been inconsistent. Inverse associations with the risk for stroke have been observed for flavonols and flavones,⁸ carotenoids,⁹ and vitamin C.^{10,11} In contrast, studies also exist in which no clear associations with dietary antioxidants were found.^{12,13} One reason for the inconsistent results may be that these studies have examined only the associations with total stroke. Different subtypes of stroke, however, have different etiopathologies¹⁴ and thus most likely also have different associations with dietary antioxidants.

The aim of this study was to examine the relation of intakes of flavonols and flavones, vitamin C, vitamin E, and carotenoids to the risk for subtypes of stroke among male smokers.

Subjects and Methods

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a double-blind, placebo-controlled, primary prevention trial undertaken to determine whether supplementation with α -tocopherol, β -carotene, or both would reduce the incidence of lung cancer in male smokers. The rationale, design, and methods of the study as well as the characteristics of the participants have been described in detail.¹⁵

The participants of the ATBC study were recruited from the total male population aged 50 to 69 years in southwestern Finland (n=290 406). To be eligible, subjects had to be smokers of at least 5 cigarettes per day at entry and to give written informed consent. The exclusion criteria included a history of cancer or other serious disease limiting long-term participation; use of vitamin E, vitamin A, or β -carotene supplements in excess of predefined doses; and treatment with anticoagulant agents.

The eligible men (n=29 133) were randomized into 1 of 4 supplementation regimens: α -tocopherol alone (daily dose 50 mg), β -carotene alone (20 mg), α -tocopherol and β -carotene, or placebo. Trial follow-up continued for 5 to 8 years (median 6.1 years).

Baseline Measurements

To establish baseline, the men completed a questionnaire on general background characteristics and medical and smoking histories. Height, weight, and blood pressure were measured, and serum

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samples were stored at -70°C . Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically (CHOD-PAP method, Boehringer Mannheim).

Dietary Assessment

Diet was assessed at baseline using a self-administered, modified diet history method.¹⁶ The diet questionnaire included 276 food items and mixed dishes. It was used with a portion-size picture booklet of 122 photographs of foods, each with 3 to 5 different portion sizes. The subject was asked to report the usual frequency of consumption and the usual portion size of foods during the previous 12 months. Frequencies were reported as the number of times per month, week, or day. At the first baseline visit, the questionnaire, along with the picture booklet, was given to the subject to be completed at home. At the second baseline visit 2 weeks later, the questionnaire was returned, reviewed, and completed with a study nurse. The questionnaire was satisfactorily completed by 27 111 participants (93%).

The food consumption data were used to compute daily nutrient intake values based on the food composition database and related software at the National Public Health Institute. Flavonol and flavone content of foods are based mainly on composition analyses done by Hertog and colleagues.^{17,18} The flavonol content of berries is, however, based on Finnish analysis.¹⁹ Total flavonol and flavone intake was calculated as the sum of intakes of quercetin, kaempferol, myricetin, luteolin, and apigenin. Carotenoid and vitamin E contents of foods are based on Finnish analyses.^{20,21}

The dietary method was validated in a pilot study carried out among 190 men before the ATBC study.¹⁶ The men completed the questionnaire first and then kept a food record for 24 days, spread over 6 months, as the reference method. They filled in the questionnaire again at the end of the study. The energy-adjusted Pearson correlations between the first dietary questionnaire and the food records were the following: flavonols and flavones 0.59, vitamin C 0.58, vitamin E 0.66, β -carotene 0.63, lutein and zeaxanthin 0.44, and lycopene 0.54.

Ascertainment of End Points

The end points of this study were cerebral infarction (CI), subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH). Only the first stroke event after randomization was registered as an end point. End points were identified from national registers by using the unique personal identification number. In Finland, all hospitalizations are registered in the Hospital Discharge Register and all deaths in the Register of Causes of Death. Both registers use the codes of the *International Classification of Diseases* (ICD), the eighth edition of which was in use until the end of 1986 and the ninth edition thereafter. The study end points comprised ICD-8 codes 430–434 and ICD-9 codes 430–431 and 433–434, excluding ICD-8 codes 431.01 and 431.91 denoting subdural hemorrhage and ICD-9 codes 4330X, 4331X, 4339X, and 4349X denoting cerebral or precerebral artery stenosis or occlusion without cerebral infarction. Utilization of the national registers also enabled identification of stroke events among study dropouts.

The validity of the stroke diagnoses in the registers has been evaluated: in a random sample ($n=546$), 90% of the stroke cases in the Hospital Discharge Register and 97% in the Register of Causes of Death retained the diagnosis of stroke in a review of clinical and autopsy data according to the criteria of the National Survey of Stroke and WHO MONICA Study.²²

Statistical Analysis

After excluding participants who at baseline reported history of stroke ($n=614$) and those who did not completely fill in the dietary questionnaire ($n=1926$), 26 497 individuals remained. The participants contributed follow-up time from the date of randomization until an end point, death, or the end of the trial (April 30, 1993). All nutrients and other antioxidants were log transformed and then energy adjusted by the regression residual method.²³ Alcohol intake was not energy adjusted. Men were grouped into quartiles of

energy-adjusted intakes of nutrients and other antioxidants. Proportional hazards models were used to estimate relative risks (RRs, with 95% CIs) of stroke associated with different intake levels of the antioxidants, with simultaneous adjustment for age, supplementation group, and cardiovascular risk factors (systolic and diastolic blood pressures, serum total cholesterol, serum HDL cholesterol, body mass index, number of smoking years, number of cigarettes daily, history of diabetes or coronary heart disease, alcohol intake, and education). Tests for linearity of the trend were obtained from the Wald test by treating median values of each quartile as continuous variables in the proportional hazards model. Interactions between antioxidant and any baseline variable were calculated by dividing the baseline values into 2 groups according to median values and using these indicators and their interaction as covariates in the proportional hazards model. The main analyses were repeated for cerebral infarction in the placebo group of the trial cohort, whereas the number of hemorrhagic strokes were too small for meaningful analyses in the placebo group only.

Results

During the 6.1-year follow-up, 736 cerebral infarctions, 83 subarachnoid hemorrhages, and 95 intracerebral hemorrhages were identified. Table 1 shows the baseline levels of selected characteristics among participants with different subtypes of stroke. Both systolic and diastolic blood pressures were higher in participants (cases) with all subtypes of stroke compared with noncases. In addition, cases of cerebral infarction were older and drank more alcohol than noncases; cases of subarachnoid hemorrhage had higher intake of energy, fat, and alcohol; and cases of intracerebral hemorrhage were older and had lower serum total cholesterol.

The median daily intakes of antioxidants were the following: flavonols and flavones 8.0 mg, vitamin C 96 mg, vitamin E 11 mg, β -carotene 1.7 mg, lutein and zeaxanthin 1.4 mg, and lycopene 0.59 mg. The highest correlation coefficients among energy-adjusted antioxidants were those between β -carotene and vitamin C ($r=0.55$), β -carotene and lutein plus zeaxanthin ($r=0.54$), flavonols/flavones and vitamin C ($r=0.50$), and vitamin C and lutein/zeaxanthin ($r=0.47$).

In the multivariate model, dietary flavonols and flavones, and vitamin E were not associated with any subtype of stroke (Table 2). Dietary vitamin C was inversely associated with risk for intracerebral hemorrhage, whereas no association was found between intake of vitamin C and risks for cerebral infarction and subarachnoid hemorrhage. β -Carotene intake was inversely associated only with the risk for cerebral infarction. Intake of lutein plus zeaxanthin was inversely associated with the risk for subarachnoid hemorrhage, and intake of lycopene inversely with the risks for cerebral infarction and intracerebral hemorrhage. Neither smoking (numbers of cigarettes per day and smoking years) nor serum total cholesterol level modified the association between intake of β -carotene and the risk for cerebral infarction.

When the multivariate models were simultaneously adjusted for other dietary antioxidants, the inverse association between β -carotene intake and cerebral infarction remained essentially unchanged (RR between the highest and lowest quartile of intake 0.77, 95% CI 0.61 to 0.99, P for trend=0.02). All other associations were attenuated such that the RR between the highest and the lowest quartile was no longer significant.

TABLE 1. Baseline Characteristics of Study Participants by Subtype of Stroke*

Characteristic	No Stroke (n=25 679)	Cerebral Infarction (n=736)	Subarachnoid Hemorrhage (n=83)	Intracerebral Hemorrhage (n=95)
Median of				
Age, y	57.0	59.7	56.5	60.2
Smoking, y	36	38	37	36
Cigarettes per day, n	20	20	20	17
Body mass index, kg/m ²	26.0	26.6	26.0	26.8
Serum cholesterol, mmol/L	6.16	6.11	6.00	5.65
HDL cholesterol, mmol/L	1.18	1.13	1.17	1.20
Systolic blood pressure, mm Hg	140	148	152	151
Diastolic blood pressure, mm Hg	88	91	94	95
Percentage of group				
Education (>11 y)	10.4	9.4	8.9	8.6
Physical activity (>2 times/wk)	19.5	18.0	15.8	14.3
Wine drinkers (≥1 glass/wk)	11.6	12.3	8.5	7.9
Tea drinkers (≥1 cup/d)	17.7	15.4	14.1	15.3
Median daily intake of				
Energy, kcal	2730	2670	2910	2680
Total fat, g	118	113	127	116
Fiber, g	24	24	25	24
Saturated fatty acids, g	49	47	53	48
Monounsaturated fatty acids, g	31	30	33	31
Polyunsaturated fatty acids, g	10	9	9	10
Trans fatty acids, g	3.0	2.9	3.2	2.9
Cholesterol, mg	540	539	549	577
Alcohol, g	11	14	16	10

*Directly age standardized to distribution of entire cohort.

In food group analysis, higher consumption of fruits was associated with reduced risk for intracerebral hemorrhage (Table 3). When further adjusted for vitamin C intake, the association became nonsignificant (RR of highest versus lowest quartile of consumption 0.57, 95% CI 0.27 to 1.21, *P* for trend=0.42). Higher consumption of vegetables was associated with lower risk for cerebral infarction. However, adjustment for β -carotene intake attenuated the association (RR 0.81, 95% CI 0.61 to 1.09, *P* for trend=0.18). In a multivariate model that simultaneously included all foods (fruits, berries, vegetables, tea, and wine), RRs for different subtypes of stroke were similar to those when the foods were included one at a time in the model.

The analyses were repeated for cerebral infarction in the placebo group of the trial cohort, and they showed similar results except for vitamin C intake and fruit consumption. The RR of the highest versus the lowest quartile for vitamin C intake was 0.66 (95% CI 0.49 to 0.99, *P* for trend=0.02) and for fruit consumption 0.59 (95% CI 0.39 to 0.89, *P* for trend=0.01). When these variables were added simultaneously to the multivariate model, their association attenuated and became nonsignificant: RRs of the highest versus the lowest quartile 0.81 (95% CI 0.49 to 1.34) and 0.67 (95% CI 0.40 to 1.11) for vitamin C intake and fruit consumption, respectively.

Discussion

Dietary β -carotene proved to be inversely associated with the risk for cerebral infarction. In addition, evidence was found for lowered risk for stroke subtypes with high intake of other carotenoids and vitamin C, but these associations lost their significance after adjustment for other dietary antioxidants. Neither flavonols nor flavones or vitamin E appeared to be related to risk.

This investigation has many strengths compared with previous studies. The validity of both the diagnoses of stroke and the dietary assessment method have been established. The end point database used permitted analysis of stroke subtypes separately. This is important, given the known differences in their etiologies.¹⁴ Nevertheless, our numbers of subarachnoid and intracerebral hemorrhages are rather small and thus more vulnerable to chance findings.

The association between the intake of vitamin E and the risk for stroke has been investigated in 3 published studies.^{8,9,24} No associations were found in any of these studies. In randomized controlled trials, vitamin E supplementation has either had no effect on stroke in patients with high risk for cardiovascular events^{25,26} or has decreased the risk for cerebral infarction while concomitantly increasing the risk for fatal hemorrhagic stroke.²⁷ Thus, more studies are needed to

TABLE 2. Intake of Dietary Antioxidants and Multivariate* Relative Risk of Subtypes for Stroke

Antioxidants by Quartile	Median Daily Intake, mg	Cerebral Infarction		Subarachnoid Hemorrhage		Intracerebral Hemorrhage	
		Cases, n	RR (95% CI)	Cases, n	RR (95% CI)	Cases, n	RR (95% CI)
Flavonols and flavones							
1st	4.2	194	1.00	25	1.00	26	1.00
2nd	6.7	184	0.99 (0.81–1.21)	21	0.89 (0.50–1.59)	27	1.08 (0.63–1.85)
3rd	9.6	177	0.96 (0.78–1.18)	20	0.87 (0.48–1.57)	18	0.70 (0.38–1.29)
4th	16.4	181	0.98 (0.80–1.21)	17	0.75 (0.40–1.41)	24	0.88 (0.50–1.57)
<i>P</i> for trend			0.81		0.39		0.41
Vitamin C							
1st	52	215	1.00	21	1.00	34	1.00
2nd	77	172	0.82 (0.67–1.00)	21	1.06 (0.58–1.95)	18	0.55 (0.31–0.97)
3rd	101	164	0.79 (0.64–0.97)	21	1.14 (0.62–2.11)	29	0.87 (0.52–1.44)
4th	141	185	0.89 (0.72–1.09)	20	1.16 (0.62–2.18)	14	0.39 (0.21–0.74)
<i>P</i> for trend			0.20		0.61		0.02
Vitamin E							
1st	7.3	217	1.00	26	1.00	30	1.00
2nd	9.6	161	0.81 (0.66–1.00)	19	0.80 (0.44–1.46)	22	0.77 (0.44–1.34)
3rd	11.8	174	0.89 (0.72–1.09)	19	0.85 (0.46–1.56)	22	0.76 (0.43–1.34)
4th	17.6	184	0.86 (0.70–1.06)	19	0.81 (0.44–1.50)	21	0.64 (0.36–1.15)
<i>P</i> for trend			0.25		0.55		0.15
β-Carotene							
1st	0.81	221	1.00	26	1.00	28	1.00
2nd	1.390	192	0.88 (0.72–1.07)	13	0.51 (0.26–1.01)	24	0.90 (0.52–1.55)
3rd	2.11	158	0.73 (0.59–0.89)	29	1.25 (0.73–2.13)	24	0.88 (0.51–1.53)
4th	3.69	165	0.74 (0.60–0.91)	15	0.67 (0.35–1.28)	19	0.66 (0.36–1.19)
<i>P</i> for trend			0.0009		0.77		0.19
Lutein+zeaxanthin							
1st	0.96	208	1.00	29	1.00	28	1.00
2nd	1.27	179	0.92 (0.75–1.12)	23	0.84 (0.49–1.47)	16	0.59 (0.32–1.09)
3rd	1.51	189	0.96 (0.79–1.18)	19	0.71 (0.40–1.28)	28	1.03 (0.60–1.75)
4th	1.88	160	0.81 (0.66–1.00)	12	0.47 (0.24–0.93)	23	0.81 (0.46–1.43)
<i>P</i> for trend			0.10		0.03		0.86
Lycopene							
1st	0.14	215	1.00	28	1.00	34	1.00
2nd	0.44	179	0.87 (0.71–1.06)	21	0.78 (0.44–1.37)	30	0.95 (0.58–1.55)
3rd	0.78	193	0.92 (0.76–1.12)	18	0.68 (0.38–1.25)	17	0.56 (0.31–1.01)
4th	1.45	149	0.74 (0.59–0.92)	16	0.63 (0.33–1.20)	14	0.45 (0.24–0.86)
<i>P</i> for trend			0.02		0.13		0.01

*Adjusted for age, supplementation group, systolic and diastolic blood pressures, serum total cholesterol, serum HDL cholesterol, body mass index, height, smoking-years, number of cigarettes daily, history of diabetes or coronary heart disease, alcohol intake, and education.

conclusively determine the effects of vitamin E on different stroke subtypes.

The association between the intake of flavonoids and the risk for stroke has been investigated in only 2 epidemiologic studies.^{8,28} In the former study,⁸ intake of flavonols and flavones was inversely associated with the risk for stroke (RR 0.27, 95% CI 0.11 to 0.70). However, the cohort was small (872 persons), and the number of stroke cases was limited (42). In the other cohort study,²⁸ no association was observed between the intake of flavonols and flavones and stroke risk (RR 1.18, 95% CI 0.70 to 2.00).

Few studies have investigated the relationship between vitamin C intake and risk for stroke. In a cohort of 730 elderly British persons (aged >65 years), vitamin C intake was inversely associated with risk (RR for the highest versus the lowest tertile of intake 0.5, 95% CI 0.3 to 0.8).¹¹ In a small Norwegian study¹⁰ that included 99 cases, intake of vitamin C was also inversely related to the risk for hemorrhagic but not ischemic stroke. Vitamin C intake was not, however, related to the risk for stroke in most of these studies.^{8,9,13} Ness and coworkers⁷ have suggested in their recent systematic review that an apparent inverse association exists between vitamin C

TABLE 3. Intake of Foods Rich in Antioxidants and Multivariate* Relative Risk of Subtypes for Stroke

	Cerebral Infarction		Subarachnoid Hemorrhage		Intracerebral Hemorrhage	
	Cases, n	RR (95% CI)	Cases, n	RR (95% CI)	Cases, n	RR (95% CI)
Vegetables†						
1st, <59 g/day	232	1.00	23	1.00	29	1.00
2nd, 59–94 g/day	177	0.78 (0.64–0.95)	24	1.06 (0.60–1.89)	31	1.14 (0.68–1.90)
3rd, 95–142 g/day	171	0.75 (0.61–0.91)	24	1.10 (0.62–1.97)	21	0.78 (0.44–1.39)
4th, >142 g/day	156	0.71 (0.57–0.87)	12	0.57 (0.28–1.17)	14	0.53 (0.27–1.02)
<i>P</i> for trend		0.001		0.21		0.04
Fruits†						
1st, <32 g/d	200	1.00	22	1.00	32	1.00
2nd, 32–70 g/d	177	0.90 (0.74–1.11)	14	0.66 (0.34–1.30)	21	0.65 (0.37–1.13)
3rd, 71–120 g/d	178	0.92 (0.75–1.13)	24	1.19 (0.67–2.14)	28	0.87 (0.52–1.45)
4th, >120 g/d	181	0.96 (0.78–1.18)	23	1.17 (0.65–2.13)	14	0.43 (0.22–0.81)
<i>P</i> for trend		0.73		0.31		0.03
Berries†						
1st, <12 g/d	222	1.00	22	1.00	28	1.00
2nd, 12–26 g/d	157	0.75 (0.61–0.92)	15	0.73 (0.38–1.42)	17	0.65 (0.35–1.19)
3rd, 27–49 g/d	189	0.91 (0.75–1.11)	25	1.28 (0.72–2.29)	26	0.98 (0.57–1.68)
4th, >49 g/d	168	0.81 (0.66–1.00)	21	1.16 (0.63–2.14)	24	0.87 (0.50–1.51)
<i>P</i> for trend		0.16		0.33		0.16
Tea						
<1 cup (170 mL)/d	617	1.00	72	1.00	77	1.00
≥1 cup/d	119	0.90 (0.74–1.09)	11	0.71 (0.38–1.35)	18	0.98 (0.58–1.65)
Wine						
<1 glass (120 mL)/wk	647	1.00	76	1.00	85	1.00
≥1 glass/wk	89	1.12 (0.89–1.43)	7	0.66 (0.30–1.49)	10	1.01 (0.50–2.03)

*Adjusted for age, supplementation group, systolic and diastolic blood pressures, serum total cholesterol, serum HDL cholesterol, body mass index, height, smoking-years, number of cigarettes daily, history of diabetes or coronary heart disease, alcohol intake, and education.

†Classification based on quartiles.

and blood pressure. In our study, both systolic and diastolic blood pressures were similar at all levels of vitamin C intake, and our multivariate models were adjusted for blood pressure (data not shown). Therefore, blood pressure cannot explain the inverse association we observed between the intake of vitamin C and the risk for intracerebral stroke in our study.

In the Health Professionals' Follow-Up Study, intake of β -carotene was inversely associated with the risk for both ischemic and hemorrhagic strokes, but the associations were not significant.⁹ In 3 other cohort studies,^{8,12,13} intake of β -carotene was unrelated to risk for stroke. Furthermore, in large-scale intervention trials β -carotene supplementation either had no effect on risk for stroke²⁹ or had no effect on the risk for cerebral infarction but increased risk for intracerebral hemorrhage.²⁷ Thus, our finding of an inverse association between β -carotene intake and cerebral infarction receives little support from other studies and may be a chance finding. Alternatively, dietary β -carotene may be a surrogate for some other dietary or lifestyle factors that are the true protectors against stroke. This is partly contradicted by the finding that after adding all dietary antioxidants to the multivariate model, only

β -carotene remained significantly associated with the risk for cerebral infarction. However, since some antioxidant intakes are moderately correlated, it is difficult to conclude their independent associations with the risk for stroke.

The present study involved male smokers. In the Health Professionals' Study,⁹ the RR for stroke in the highest quintile of β -carotene intake compared with the lowest quintile was 0.29 among current smokers, whereas the respective RR was 1.20 among never-smokers, but neither group showed a significant trend. Whether dietary β -carotene is inversely associated with the risk for stroke only among smokers needs further confirmation. However, null effects in controlled trials contradicts this possibility.^{27,29} The generalizability of our results applies, of course, also to other antioxidants. It is possible that the effects of antioxidants in general are different in smokers compared with nonsmokers. Therefore, our results cannot be generalized to nonsmokers.

Epidemiologic data for other carotenoids are scant. Lutein intake was inversely associated with the risk for ischemic but not hemorrhagic stroke in one cohort study.⁹ The intake of lycopene was not associated with the risk for either ischemic stroke or hemorrhagic stroke.⁹

The majority of epidemiological studies on consumption of fruits and vegetables and stroke risk have reported an inverse association. We found that consumption of vegetables was inversely associated with the risk for cerebral infarction, and the consumption of fruits was inversely associated with the risk for intracerebral hemorrhage. When intake of β -carotene and vitamin C, respectively, were added to the multivariate models, both associations attenuated but a moderate nonsignificant association still remained. This suggests that in addition to β -carotene in vegetables and vitamin C in fruit, other dietary factors in these foods provide protection against stroke.

In conclusion, high intake of β -carotene was associated with decreased risk for cerebral infarction in male smokers. This finding is, however, not supported by other studies and must therefore be interpreted cautiously. In addition, no consistent associations were found between other dietary antioxidants and stroke subtypes. The protective association between fruit and vegetable consumption and risk for stroke was confirmed.

References

- Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol*. 1997;26:1–13.
- Joshihura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA*. 1999;282:1233–1239.
- Sies H, Stahl W, Vitamins E, and C, β -carotene, and other carotenoids as antioxidants. *Am J Clin Nutr*. 1995;62(suppl):1315S–1321S.
- Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet*. 1994;344:793–795.
- Gryglewski RJ, Korbut R, Robak J, Swies J. On the mechanism of antithrombotic action of flavonoids. *Biochem Pharmacol*. 1987;36:317–321.
- Williams JC, Forster LA, Tull SP, Ferns GA. Effects of vitamin E on human platelet and mononuclear cell responses in vitro. *Int J Exp Pathol*. 1999;80:227–234.
- Ness AR, Chee D, Elliott P. Vitamin C and blood pressure: an overview. *J Hum Hypertens*. 1997;11:343–350.
- Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke. *Arch Intern Med*. 1996;156:637–642.
- Ascherio A, Rimm EB, Hernán MA, Giovannucci E, Kawachi I, Stampfer MJ, Willett WC. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. *Ann Intern Med*. 1999;130:963–970.
- Vollset SE, Bjelke E. Does consumption of fruit and vegetables protect against stroke? *Lancet*. 1983;2:742. Letter.
- Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. *BMJ*. 1995;310:1563–1566.
- Daviglus ML, Orenca AJ, Dyer AR, Liu K, Morris DK, Persky V, Chavez N, Goldberg J, Drum M, Shekelle RB, Samler J. Dietary vitamin C, β -carotene and 30-year risk of stroke: results from the Western Electric Study. *Neuroepidemiology*. 1997;16:69–77.
- Ross RK, Yuan J-M, Henderson BE, Park J, Gao Y-T, Yu MC. Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. *Circulation*. 1997;96:50–55.
- Leppälä JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: associations of blood pressure, cholesterol, and antioxidants. *Stroke*. 1999;30:2535–2540.
- The ATBC Cancer Prevention Study Group. The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study: design, methods, participant characteristics, and compliance. *Ann Epidemiol*. 1994;4:1–10.
- Pietinen P, Hartman AM, Haapa E, Räsänen L, Haapakoski J, Palmgren J, Albanes D, Virtamo J, Huttunen JK. Reproducibility and validity of dietary assessment instruments. I: a self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol*. 1988;128:655–666.
- Hertog MG, Hollman PC, Katan MB. Content of potentially anticarcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. *J Agric Food Chem*. 1992;40:2379–2383.
- Hertog MG, Hollman PC, van de Putte P. Content of potentially anticarcinogenic flavonoids in tea infusions, wines, and fruit juices. *J Agric Food Chem*. 1993;41:1242–1246.
- Häkkinen SH, Kärenlampi SO, Heinonen IM, Mykkänen HM, Törrönen AR. Content of the flavonols quercetin, myricetin and kaempferol in 25 edible berries. *J Agric Food Chem*. 1999;1999:47:2274–2279.
- Piironen V. Tocopherols and tocotrienols in foods and in the average diet. Helsinki, Finland: Helsinki University; 1986.
- Heinonen M. Carotenoids and retinoids in Finnish foods and the average diet. Helsinki, Finland: Helsinki University; 1990.
- Leppälä JM, Virtamo J, Heinonen OP. Validation of stroke diagnosis in the National Hospital Discharge Register and the Register of Causes of Death in Finland. *Eur J Epidemiol*. 1999;15:155–160.
- Willett WC. *Nutritional Epidemiology*. New York, NY: Oxford University Press; 1990.
- Kok FJ, Vermeeren R, Hofman A, van Laar A, de Bruin M, Hermus RJ, Valkenburg HA. Serum selenium, vitamin antioxidants, and cardiovascular mortality: a 9-year follow-up study in the Netherlands. *Am J Clin Nutr*. 1987;45:462–468.
- The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:154–160.
- GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354:447–455.
- Leppälä JM, Virtamo J, Fogelholm R, Huttunen JK, Albanes D, Taylor PR, Heinonen OP. Controlled trial of α -tocopherol and β -carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol*. 2000;20:230–235.
- Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *Am J Epidemiol*. 1999;149:943–949.
- Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett WC, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145–1149.